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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1642	28

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/410,336	Applicant(s) LOVE ET AL.	
	Examin r Stephen L. Rawlings, Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The amendment filed August 7, 2003 in Paper No. 27 has been entered. Claims 1, 5, 9, 10, 13, and 14 have been amended.

2. Claims 1-16 are pending in the application and are currently under prosecution.

Grounds of Objection and Rejection Withdrawn

3. Unless specifically reiterated below, the grounds of objection and rejection set forth in the previous Office action mailed May 7, 2003 (Paper No. 26) have been withdrawn.

For clarity of record, the rejection of claims 1-8 under 35 U.S.C. 112, second paragraph, as being incomplete because claims 1 and 5 omit one or more essential steps, such omission amounting to a gap between the steps, for the reason set forth in the preceding Office Action mailed May 7, 2003 (Paper No. 26) has been withdrawn because Applicants have amended claims 1 and 5 to recite a step in which the presence of the identifying agent, or a compound comprising an identifying agent is detected. Applicants have argued that claims 1 and 5 need not recite a step in which the data acquired in the detection step is correlated with the subject's anatomy to determine the location of the premalignant or malignant breast cancer cells within the breast duct or breast ductal network. As claims 1 and 5 presently recite a step in which in which the presence of the identifying agent, or a compound comprising an identifying agent is detected, it is believed clear that in practicing the claimed method to identify the location of premalignant or malignant breast cancer cells within the breast duct, breast ductal network, the practitioner would necessarily have to correlate the data acquired in the detection step with the subject's anatomy to determine the location of the premalignant or malignant breast cancer cells within the breast duct or breast ductal network.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 5-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reason set forth in section 7 of the Office action mailed May 7, 2003 (Paper No. 26).

Claim 5 recites the term "cancer cell specific identifying agent"; however, there does not appear to be proper and sufficient antecedent basis in the specification to support the recitation of this term in the claims.

Applicants have traversed this ground of rejection in Paper No. 27 arguing that the specification, as originally filed, need not provide *ipsis verbis* support for the language set forth in the claims. Furthermore, Applicants have asserted that sufficient support can be found in the specification at page 10, lines 23-34, and at page 11, lines 13 and 14.

Applicants' arguments have been carefully considered but not found persuasive. Applicants are correct; the specification, as originally filed, need not provide *ipsis verbis* support for the language set forth in the claims. However, implicit or inherent, if not express support for the claim language must exist in the specification, as originally filed.

Contrary to Applicants' assertions, the disclosure at page 10, lines 23-34, fails to provide proper and sufficient written support for the recitation of the term "cancer cell specific identifying agent". As noted in the previous Office action, at page 10, the specification discloses, "the identifying agent will be specific for a cell membrane bound target" (lines 27 and 28), but the disclosure at page 10, lines 23-34, fails to suggest that such a target might be a cancer-specific target. A cell membrane bound target is not necessarily a cancer-specific target; moreover, it would not be understood by the skilled

artisan that the identifying agent that binds a cell membrane bound target is cancer-specific. Accordingly, the disclosure to which Applicants have referred does not provide proper and sufficient support for a recitation of a requirement that the identifying agent be specific for cancer cells. As also noted in the previous Office action, the examples of identifying agents set forth in the disclosures on pages 14 and 15 do not provide adequate support for the breadth of the claim language. In particular, the disclosed examples of identifying agents fail to provide the necessary express, implicit, or inherent support because, for example, the identifying agents that are antibodies bind antigens, such as ErbB-2, which are not cancer cell specific.

Contrary to Applicants' assertion, the disclosure at page 11, lines 13 and 14, also fails to provide adequate support. The disclosure to which Applicants have referred reads, "the identifying agent may in and of itself be capable of binding a targeting agent thereby providing identification through visualization" (Specification, page 11, lines 13 and 14). This disclosure does not suggest that the identifying agent can be cancer-cell specific.

Furthermore, contrary to Applicants' assertion, because of the inadequacy of the written description contained within the specification, as originally filed, it would not be understood by the skilled artisan that Applicants had possession of the claimed invention.

Again, this issue might be resolved if Applicants can point to specific disclosures in the specification that are believed to provide the necessary support, or alternatively amend the claims to recite the explicit language set forth in the specification. For example, Applicants might obviate this ground of rejection by amending claim 5 to recite, "providing an identifying agent specific for a cell membrane bound target", rather than "providing a premalignant or malignant cancer cell specific identifying agent".

6. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 5, 9, and 13 recite, "allowing [...] unbound portions of the delivered [compound or identifying agent] to be eliminated from said at least one duct". Additionally, claims 9 and 13 recite, "determining the lymph node involvement after said unbound portions of the delivered [compound or identifying agent] are no longer present within said at least one breast duct"; and as newly amended, claims 1 and 5 recite, "after said unbound portions of the delivered compound [or identifying agent] are no longer present within the said at least one breast duct". However, there does not appear to be proper and sufficient antecedent basis in the specification to support the recitation of these limitations in the claims.

Applicants have traversed this ground of rejection in Paper No. 27 arguing the specification provides the necessary support.

Applicants' arguments have been carefully considered but not found persuasive.

Applicants have remarked that the specification, including the examples, provides support for the claim language. However, it is unclear which particular disclosures set forth in the specification Applicants believe provides the necessary support for the recitation of the steps of "*allowing* [...] *unbound portions of the delivered [compound or identifying agent] to be eliminated from said at least one duct*" and "determining the lymph node involvement [or detecting the presence of the compound or identifying agent bound to premalignant or malignant cells within a duct or the ductal network] *after said unbound portions of the delivered [compound or identifying agent] are no longer present within said at least one breast duct*".

As noted in the previous Office action, the specification discloses, "the assessed breasts were washed with saline solution to remove nonspecifically bound immunoliposomes" (page 16, lines 30 and 31; and page 17, lines 28 and 29); however, these disclosures do not appear to provide the necessary express, implicit, or inherent support. Allowing the delivered compound or identifying agent to be eliminated is a passive process step, whereas the disclosed step of washing the assessed breasts with saline solution to remove nonspecifically bound immunoliposomes is an active step. The disclosure at page 16 does not expressly, implicitly, or inherently support the recitation of the passive step of allowing the delivered compound or identifying agent to

be eliminated from the at least one duct through which the compound or identifying agent is delivered. Therefore, the recitations of these limitations in the present claims appear to introduce new matter and thereby violate the written description requirement set forth under 35 USC § 112, first paragraph.

These issues might be resolved if Applicants were to point to specific disclosures that are believed to provide adequate support for the recitation of these limitations in the present claims.

Alternatively, Applicants might remedy this ground of rejection by amending claims 1, 5, 9, and 13 to recite, for example, a step comprising washing the assessed breast ducts with saline solution to remove nonspecifically bound said identifying agent or said compound comprising an identifying agent, support for which is found in the specification, e.g., at page 16, lines 30 and 31.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 9-16 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete because claims 9 and 13 omit one or more essential steps, such omission amounting to a gap between the steps for the reason stated in section 12 of the previous Office Action mailed May 7, 2003 (Paper No. 26).

Applicants have traversed these grounds of rejection reiterating the arguments set forth in reply to previous Office actions but have additionally remarked: "No amendment was need to claims 9 and 13 in view of the already recited 'determining' step".

Applicants' arguments have again been carefully considered but not found persuasive.

In traversing this rejection, Applicants have noted that MPEP § 2172.01 states that essential matter is defined as elements, steps or the like that are described by the Applicants in the specification as essential to practicing the invention. The same section of the MPEP has been cited in the previous Office actions to support the

maintenance of these grounds of rejection. As noted in the Office action mailed May 7, 2003, because the specification teaches that the omitted steps are essential to the practice of the invention, the omission of these essential steps in the claims are proper grounds for the rejection of those claims under 35 USC § 112, second paragraph. Thus, in answer to Applicant's query, the "authority" for the position of the Office is the MPEP, which at § 2172.01 states:

> A claim which omits matter disclosed to be essential to the invention as described in the specification or in other statements of record may be rejected under 35 U.S.C. 112, first paragraph, as not enabling. *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). See also MPEP § 2164.08(c). Such essential matter may include missing elements, steps or necessary structural cooperative relationships of elements described by the applicant(s) as necessary to practice the invention.
>
> In addition, a claim which fails to interrelate essential elements of the invention as defined by applicant(s) in the specification may be rejected under 35 U.S.C. 112, second paragraph, for failure to point out and distinctly claim the invention. See *In re Venezia*, 530 F.2d 956, 189 USPQ 149 (CCPA 1976); *In re Collier*, 397 F.2d 1003, 158 USPQ 266 (CCPA 1968). >But see *Ex parte Nolden*, 149 USPQ 378, 380 (Bd. Pat. App. 1965) ("[I]t is not essential to a patentable combination that there be interdependency between the elements of the claimed device or that all the elements operate concurrently toward the desired result"); *Ex parte Huber*, 148 USPQ 447, 448-49 (Bd. Pat. App. 1965) (A claim does not necessarily fail to comply with 35 U.S.C. 112, second paragraph where the various elements do not function simultaneously, are not directly functionally related, do not directly intercooperate, and/or serve independent purposes.).

Applicants have argued that it is not necessary to provide factual evidence that the steps are not essential, as the teachings of the specification suggest; rather Applicants have argued that the burden is upon the Office to show that essential steps have been omitted. In reply to this argument, the specification teaches that the omitted steps are essential, since all examples set forth therein teach the necessity of detecting the identifying agent or targeting agent coupled to an identifying agent by MRI and correlating the data so acquired with information gained by repeated physical examination and/or mammogram to assign a location to the pre-malignant or malignant cells within lymph nodes.

In reply to Applicants' remark that because claims 9 and 13 recite a "determining" step, the claims do not have to recite a "detecting" step. Upon consideration, while the recitation of the "determining" step would reasonably guide the practitioner of the

claimed method to correlate the data acquired in a detection step with the subject's anatomy to determine the location of the premalignant or malignant breast cancer cells within the lymph nodes, claims 9 and 13 do not recite a "detecting" step. The disclosure teaches the necessity of detecting the identifying agent or targeting agent coupled to an identifying agent. Therefore, because the claims do not recite a "detecting" step, the claims fail to interrelate essential elements of the invention, namely the elements of providing, delivering, and allowing the identifying agent or a compound comprising an identifying agent to bind to premalignant or malignant cell or to be passively eliminated from the breast duct, and determining lymph node involvement.

Amending claims 9 and 13 to recite a "detecting" step can obviate this ground of rejection.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hou et al. (*Radiology* **195**: 568-569, 1995) in view of Canto et al. (*Gastrointestinal Endoscopy* **44**: 1-7, 1996).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 5-8 are drawn to a method of identifying the location of premalignant or malignant breast cancer within a breast duct or breast ductal network, wherein said method comprises:

(a) providing a cancer cell specific identifying agent that is cancer cell specific within the breast duct or breast ductal network;

(b) delivering the agent through at least one breast duct, wherein said step of delivering the agent comprises cannulation or catheterization of the breast duct (claim 6) or wherein said agent is delivered to more than one duct on a breast (claim 7);

(c) allowing the identifying agent to bind to premalignant or malignant breast cancer cells within the at least one breast duct or breast ductal network and allowing unbound portions of the identifying agent to be eliminated from the at least one breast duct;

(d) detecting the presence of the identifying agent bound to premalignant or malignant breast cancer cells within the at least one breast duct or breast ductal network after the unbound portions of the identifying agent are no longer within the at least one breast duct; and

(e) identifying the location of the premalignant or malignant breast cancer cells bound to the identifying agent within the at least one breast duct or breast ductal network;

wherein the cells are identified for the purpose of excising tissue surrounding and including the cells (claim 8).

Teachings or Suggestions of the Primary Reference

Hou et al. teaches a method comprising providing a pre-malignant or malignant cancer cell specific identifying agent, namely methylene blue. Hou et al. teaches delivering the identifying agent through at least one breast duct by cannulation or catheterization of the one or more breast ducts. Hou et al. teaches allowing the

delivered identifying agent to bind pre-malignant or malignant cells within the breast duct or breast ductal network. Hou et al. teaches identifying the location of the pre-malignant or malignant cell bound to the identifying agent within the breast duct or breast ductal network. Hou et al. teaches that the identifying agent was injected into the patient through a breast duct in a sufficient amount to facilitate localization of a breast lesion before surgical excision was performed to remove the pre-malignant or malignant cancerous cells from the patient.

Although Hou et al. does not explicity teach methylene blue is a pre-malignant or malignant cancer cell specific identifying agent, the specification does not define the term "cancer specific identifying agent". Accordingly, as also noted in the previous Office action mailed May 7, 2003 (Paper No. 26), the American Heritage® Dictionary of the English Language: 4th Edition defines "specific" as "[r]elating to, characterizing, or distinguishing a species" (Copyright © 2000 by Houghton Mifflin Company). Thus, a "cancer specific identifying agent" in the context of the claim would be reasonably defined as an identifying agent that distinguishes breast cancer tissue from normal breast tissue in the breast duct or breast ductal network. Canto et al. teaches methylene blue is capable of binding selectively to pre-malignant, or dysplastic cells, and to malignant cells. Therefore, because methylene blue selectively stains pre-malignant or malignant tissue differentially relative to normal tissue within the breast duct or breast ductal network and enables the clinician to distinguish pre-cancerous and cancerous tissue from normal tissue within the breast duct or breast ductal network, it would appear that methylene blue is a "cancer cell specific identifying agent that is cancer cell specific within the breast duct or breast ductal network", as recited in claim 5. This conclusion is supported Hou et al., which states, "the duct and any involved lobules could be identified by the presence of the blue dye" (page 568, column 3). Hou et al. discloses that pre-malignant or malignant cells within the breast duct or breast ductal network were identified by virtue of the binding of the identifying agent, namely methylene blue to the cells. Moreover, the term "cancer specific identifying agent" is not defined in the specification, but the guidance set forth in the specification suggests the identifying agent does not have to bind *exclusively* to cancer cells. The specification

provides examples of monoclonal antibodies that are presumed to be suitable "cancer specific identifying agents". One of these identifying agents is a monoclonal antibody that binds ErbB-2, which can be used to identify cancer cells; but cancer cells alone do not express ErbB-2, since normal cells also express the antigen. Therefore, the present claims do not read on a method comprising delivering an identifying agent that binds *exclusively* to cancer cells.

Differences between the Teachings or Suggestions of the Primary Reference and the Claims at Issue

Hou et al. does not expressly disclose allowing any unbound identifying agent to be eliminated by natural absorption and clearance in the body so that its removal by the practitioner is not required, as recited in claim 5. Furthermore, Hou et al. does not expressly teach that the identifying agent, which is bound to premalignant or malignant cells within the breast duct or breast ductal network can, or should be detected after the unbound portions of the identifying agent or compound are no longer present within the breast duct, as recited in claim 5.

Although Hou et al. does not explicitly teach allowing unbound portions of the delivered identifying agent to be eliminated from the breast duct, the elimination of the unbound portions of the identifying agent will occur naturally as a result of the process. The step of *allowing* the unbound portions of the delivered identifying agent to be eliminated appears to be a passive step, i.e., allowing unbound portions to be eliminated appears to require no active step or participation by the practitioner. Practicing the method of Hou et al. will intrinsically lead to allowing unbound identifying agent to be eliminated by natural processes, i.e., passive diffusion from the breast duct or breast ductal network into the lymphatic system and passive diffusion from the lymphatic system to the blood, which carries the unbound identifying agent to organs, e.g., liver and kidney, which act to "clear" the body of the unbound identifying agent.

Teachings and Suggestions of the Secondary Reference and the Level of Ordinary Skill in the Pertinent Art

Canto et al. teaches methylene blue is capable of binding selectively to pre-malignant, or dysplastic cells, and to malignant cells; Canto et al. demonstrates that methylene blue can be used to distinguish and localize premalignant or malignant epithelial cancer cells. Canto et al. teaches that after the step of delivering methylene blue and allowing methylene blue to bind premalignant or malignant cells, the tissue is washed to remove excess methylene blue. See entire document, but particularly the methods and materials section at page 2.

Therefore, although Hou et al. does not expressly teach that the identifying agent, which is bound to premalignant or malignant cells within the breast duct or breast ductal network can, or should be detected after the unbound portions of the identifying agent or compound are no longer present within the breast duct, as recited in claim 5, the level of skill in the art at the time the invention was made was such that it would have been obvious to one of ordinary skill in the art to detect in a breast duct or breast ductal network, the presence of premalignant or malignant breast cancer cells, which are bound by an identifying agent, *after* washing the breast tissue to remove any unbound, or non-specifically bound identifying agent and/or *after* allowing any unbound bound identifying agent to passively diffuse out of the tissue. Canto et al., for example, teaches that *before* detecting premalignant or malignant cancer cells bound to the identifying agent, the excess, unbound identifying agent should be washed away from the anatomical site of the suspected lesion. Only after excess, unbound identifying agent is washed off, do Canto et al. disclose that the location of premalignant or malignant cancer cells bound by the identifying agent is determined. Therefore, it would have been understood by the artisan of ordinary skill at the time of invention that the presence of the unbound or non-specifically bound identifying agent in the tissue might produce undesirable levels of background, obscure detection of the premalignant or malignant cells within the tissue, and lead to false negative and/or false positive results.

The Obviousness of the Claimed Invention

In view of the prior art, as a whole, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to practice the method of Hou et al. to detect in a breast duct or breast ductal network, the presence of premalignant or malignant breast cancer cells, which are bound by an identifying agent, *after* washing the breast tissue to remove any unbound, or non-specifically bound identifying agent and/or *after* allowing any unbound bound identifying agent to passively diffuse out of the tissue, because Canto et al., for example, teaches that *before* detecting premalignant or malignant cancer cells bound to the identifying agent, the excess, unbound identifying agent should be washed away from the anatomical site of the suspected lesion and it would have been understood by the artisan of ordinary skill at the time of invention that the presence of the unbound or non-specifically bound identifying agent in the tissue might produce undesirable levels of background, obscure detection of the premalignant or malignant cells within the tissue, and lead to false negative and/or false positive results.

One of ordinary skill in the art at the time the invention was made would have been motivated practice the method of Hou et al., because Hou et al. teaches the method can be used to localize premalignant and malignant breast cancer cells within a breast duct or breast ductal network to facilitate surgical resection of the cells in the process of treating a patient having such cells.

Response to Applicants' Remarks

Applicants have traversed the rejection of claims 5-8 under 35 USC § 102(b) for the reason set forth in section 15 of the previous Office action mailed May 7, 2003 (Paper No. 26). To the extent that Applicants' remarks might apply to a traversal of this ground of rejection, Applicants' remarks have been carefully considered, but not found persuasive.

The Examiner disagrees with Applicants' assertion, "if methylene blue were allowed to pass into other parts of the body, the portions of the body that received the eliminated methylene blue would be erroneously marked for removal from the body of

the patient" (Paper No. 27, page 14). The prior art teaches that this assertion lacks a reasonable basis.

The Examiner disagrees with Applicants' assertion, "methylene blue is not used [...] to identify the location of premalignant or malignant [breast cancer] cells" (Paper No. 27, page 15) in the breast duct or breast ductal network. Methylene blue selectively stains premalignant and malignant epithelial cancer cells to facilitate localization and surgical resection of the cells, as evidenced by the teachings of Canto et al. and Hou et al. The clinical utility of methylene blue in localizing epithelial cancer lesions, including breast cancer, was conventional at the time the invention was made as further evidenced by the teachings of Dietler et al. (*Am. Surg.* **42**: 810-811, 1976), Gill et al. (*Cancer* **53**: 2724-2727, 1984), and Love et al. (*Lancet* **348**: 997-999, 1996). *Arguendo*, if, as Applicants have remarked methylene blue is only used to identify the boundary of the duct that needs removal, then methylene blue is used to identify the location of premalignant or malignant breast cancer cells in a breast duct or breast ductal network.

Applicants' have also reiterated arguments, which were set forth in reply to previous Office actions, e.g., methylene blue is not a cancer cell specific identifying agent. The merit of these arguments has again been carefully considered, but not found persuasive for the reasons set forth herein and/or in the previous Office actions.

11. Claims 1-4 and 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allan et al. *(British Journal of Cancer* **67**: 706-712, 1993) in view of Krag et al. (*New England Journal of Medicine* **339**: 941-946, 1998), Hou et al. (*Radiology* **195**: 568-569, 1995), Canto et al. (*Gastrointestinal Endoscopy* **44**: 1-7, 1996), and Vitetta et al. (*Cancer Research* **54**: 5301-5309, 1994).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-4 are drawn to a method of identifying the location of premalignant or malignant breast cancer within a breast duct or breast ductal network, wherein said method comprises:

(a) providing an identifying agent coupled to a targeting molecule (claim 1);

(b) delivering the agent through at least one breast duct, wherein said step of delivering the agent comprises cannulation or catheterization of the breast duct (claim 2) or wherein said agent is delivered to more than one duct on a breast (claim 3);

(c) allowing the identifying agent to bind to premalignant or malignant breast cancer cells within the at least one breast duct or breast ductal network and allowing unbound portions of the identifying agent to be eliminated from the at least one breast duct;

(d) detecting the presence of the identifying agent bound to premalignant or malignant breast cancer cells within the at least one breast duct or breast ductal network after the unbound portions of the identifying agent are no longer within the at least one breast duct; and

(e) identifying the location of the premalignant or malignant breast cancer cells bound to the identifying agent within the at least one breast duct or breast ductal network;

wherein the cells are identified for the purpose of excising tissue surrounding and including the cells (claim 4).

Claims 9-16 are drawn to a method of determining the lymph node involvement in patients diagnosed with premalignant or malignant breast cancer, wherein said method comprises:

(a) providing an identifying agent (claim 13), which can be coupled to a targeting molecule (claim 9);

(b) delivering the agent through at least one breast duct, wherein said step of delivering the agent comprises cannulation or catheterization of the breast duct (claims 11 and 15) or wherein said agent is delivered to more than one duct on a breast (claims 12 and 16);

(c) allowing the identifying agent to bind to premalignant or malignant breast cancer cells within the at least one breast duct or breast ductal network and allowing unbound portions of the identifying agent to be eliminated from the at least one breast duct;

(d) determining lymph node involvement after the unbound portions of the identifying agent are no longer within the at least one breast duct; and

(e) identifying the location of the lymph node involved;

wherein detecting lymph node involvement comprises detecting the agent in a sentinel lymph node (claims 10 and 14).

Teachings and Suggestions of the Primary Reference

Allan et al. teaches a method for identifying the location of premalignant or malignant breast cancer cells within a breast duct or breast ductal network, wherein said method comprises providing a compound comprising a targeting molecule coupled to an identifying agent, i.e., a radiolabeled anti-ErbB2 antibody, delivering the compound, allowing the delivered compound to bind to premalignant or malignant breast cancer cells within said at least one breast duct or breast ductal network, detecting the presence of the compound bound to premalignant or malignant cells within said at least one breast duct or breast ductal network, and identifying the location of the premalignant or malignant breast cancer cells bound to said compound within said at least one breast duct or breast ductal network (claims 1 and 5). Allan et al. teach or suggest the location of the premalignant or malignant breast cancer cells is identified for the purpose of excising tissue surrounding and including the cells (claims 4 and 8). Additionally, Allan et al. teaches a method for determining lymph node involvement in patients diagnosed with premalignant or malignant breast cancer, wherein said method comprises providing a compound comprising a targeting molecule coupled to an

identifying agent, i.e., a radiolabeled anti-ErbB2 antibody, delivering the compound, allowing the delivered compound to bind to premalignant or malignant breast cancer cells within said lymph node, determining the presence of the compound bound to premalignant or malignant cells within said lymph node, and identifying the location of said lymph node (claims 9 and 13). See the entire document, including the abstract, methods and materials, results and discussion. See the previous Office action.

Although Allan et al. does not expressly disclose detecting the identifying agent in a sentinel lymph node (claims 10 and 14), Allan, et al discloses, "two patients had strong membrane staining and provided excellent tumor localisation to both breast primary and regional node metastases" (abstract). Krag et al. teaches an example of a regional lymph node is a sentinel lymph node (abstract). Also, Krag et al. teaches that if regional node metastases have been detected in a patient, the sentinel lymph node would be involved, because the sentinel lymph node is "the first stop along the route of lymphatic drainage from a primary tumor" (page 941, column 2). Therefore, Allan et al. teaches the disclosed method can be used to successfully detect and localize malignant breast cancer cells in a sentinel lymph node in a patient diagnosed with breast cancer.

Differences between the Teachings or Suggestions of the Primary Reference and the Claims at Issue

Allan et al. does not expressly teach that the identifying agent or compound comprising an identifying agent, which is bound to premalignant or malignant cells within the breast duct or breast ductal network can, or should be detected after the unbound portions of the identifying agent or compound are no longer present within the breast duct, as recited in claims 1, 9, and 13. Allan et al. does not expressly teach or suggest delivering the compound through one or more breast ducts (claims 1, 3, 9, 12, 13, and 16) by a process that comprises cannulation or catheterization of the breast duct (claims 2, 6, 11, and 15).

Although Allan et al. does not explicitly teach allowing unbound portions of the delivered identifying agent or compound comprising an identifying agent to be eliminated from the breast duct or lymph node, the elimination of the unbound portions

of the agent or compound will occur naturally as a result of the process. The step of *allowing* the unbound portions of the delivered agent or compound to be eliminated appears to be a passive step, i.e., allowing unbound portions to be eliminated appears to require no active step or participation by the practitioner. Practicing the method of Allan et al. will intrinsically lead to allowing unbound identifying agent to be eliminated by natural processes, i.e., passive diffusion from the breast duct or breast ductal network into the lymphatic system and passive diffusion from the lymphatic system to the blood, which carries the unbound identifying agent to organs, e.g., liver and kidney, which act to "clear" the body of the unbound identifying agent.

Teachings and Suggestions of the Secondary Reference and the Level of Ordinary Skill in the Pertinent Art

Canto et al. teaches methylene blue is capable of binding selectively to pre-malignant, or dysplastic cells, and to malignant cells; Canto et al. demonstrates that methylene blue can be used to distinguish and localize premalignant or malignant epithelial cancer cells. Canto et al. teaches that after the step of delivering methylene blue and allowing methylene blue to bind premalignant or malignant cells, the tissue is washed to remove excess methylene blue. See entire document, but particularly the methods and materials section at page 2.

Therefore, although Allan et al. does not expressly teach that the identifying agent, which is bound to premalignant or malignant cells within the breast duct or breast ductal network can, or should be detected after the unbound portions of the identifying agent or compound are no longer present within the breast duct, as recited in claim 5, the level of skill in the art at the time the invention was made was such that it would have been obvious to one of ordinary skill in the art to detect in a breast duct or breast ductal network, the presence of premalignant or malignant breast cancer cells, which are bound by an identifying agent, *after* washing the breast tissue to remove any unbound, or non-specifically bound identifying agent and/or *after* allowing any unbound bound identifying agent to passively diffuse out of the tissue. Canto et al., for example, teaches that *before* detecting premalignant or malignant cancer cells bound to the

identifying agent, the excess, unbound identifying agent should be washed away from the anatomical site of the suspected lesion. Only after excess, unbound identifying agent is washed off, do Canto et al. disclose that the location of premalignant or malignant cancer cells bound by the identifying agent is determined. Therefore, it would have been understood by the artisan of ordinary skill at the time of invention that the presence of the unbound or non-specifically bound identifying agent in the tissue might produce undesirable levels of background, obscure detection of the premalignant or malignant cells within the tissue, and lead to false negative and/or false positive results.

Hou et al. teaches identifying the location of the pre-malignant or malignant cell bound to the identifying agent within the breast duct or breast ductal network by delivering the identifying agent through at least one breast duct by cannulation or catheterization of the one or more breast ducts. Hou et al. teaches allowing the delivered identifying agent to bind pre-malignant or malignant cells within the breast duct or breast ductal network. Hou et al. teaches that the identifying agent was injected into the patient through a breast duct in a sufficient amount to facilitate localization of a breast lesion before surgical excision was performed to remove the pre-malignant or malignant cancerous cells from the patient. See entire document.

Vitetta et al. teaches that there are limitations in the use of monoclonal antibodies in cancer therapy but, in particular, monoclonal antibodies that are administered to a patient intravenously may not be able to gain access to a tumor for a variety of reasons, including poor and heterogeneous tumor vascularization and selective binding of monoclonal antibody to tumor cells closest to the blood supply. Another potential drawback is that when a patient is administered heterologous antibodies, an immune response to the antibodies may preclude the efficacy of further courses of therapy (page 5305, column 2). Although, the teachings of Vitetta et al. are specifically drawn to methods of therapy, the issues presented here are equally relevant to methods of diagnosis and breast cancer staging, wherein monoclonal antibodies are used to target identifying agents to particular cells and tissues.

The Obviousness of the Claimed Invention

In view of the prior art, as a whole, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Allan et al. by delivering the identifying agent through at least one breast duct according to the method of Hou et al., because Vitetta et al. teaches monoclonal antibodies, which are administered to a patient intravenously, may not be able to gain access to a tumor because, for example, the tumor may be poorly vascularized, whereas monoclonal antibodies comprising an identifying agent, which are administered through one or more breast ducts, are delivered to the precise location of the suspected cancerous lesions in the breast duct and breast ductal network, such that the monoclonal antibody can make contact the cancerous lesion without need of passing through the blood. Furthermore, it would have been understood by one of ordinary skill in the art at the time the invention was made that the method of Hou et al. enables one to deliver the identifying agent directly to the targeted site at which the cells are expected to occur in a patient without undue risk of retention of the identifying agent in tissues where the cells are not expected to be found and without undue risk that at least a portion of the identifying agent will naturally clear the patient's body before it reaches the breast ductal network via the blood stream, as might occur if the identifying agent were administered intravenously. Therefore, it would have been understood by one of ordinary skill in the art at the time the invention was made that delivery of the identifying agent by cannulation of a breast duct could enable the clinician to image the tumor without risking harm to the patient by delivering unnecessarily large quantities of antibodies and radioisotopes that may have adverse effects.

One would have been motivated to modify the method of Allen et al. by delivering the identifying agent using the method of Hou et al. because the modification would provide an advantage to the clinician because delivering the identifying agent according to the method of Hou et al. enables one to deliver the identifying agent directly to the targeted site at which the cells are expected to occur in a patient without undue risk of retention of the identifying agent in tissues where the cells are not expected to be found

and without undue risk that at least a portion of the identifying agent will naturally clear the patient's body before it reaches the breast ductal network via the blood stream, as might occur if the identifying agent were administered intravenously. Furthermore, one would have been motivated to modify the method of Allen et al. by delivering the identifying agent using the method of Hou et al. because the modification would provide an additional advantage to the clinician, because the clinician could image the tumor without risking harm to the patient by having to deliver unnecessarily large quantities of antibodies and radioisotopes that may have adverse effects.

Response to Applicants' Remarks

Applicants have traversed the rejection of claims 1-16 under 35 USC § 103(a) for the reason set forth in section 17 of the previous Office action mailed May 7, 2003 (Paper No. 26), arguing, in particular, no motivation would have existed to combine the teachings of the cited references, impermissible hindsight had to have been used in determining the obviousness of the invention, no reasonable expectation of successfully practicing the invention would have been had by one of ordinary skill in the art at the time the invention was made, and the steps needed to prepare the agent disclosed by Allan et al. "contradict" the method of Hou et al.

Applicants' remarks have been previously considered and were and still not found persuasive; therefore Applicants are referred to the preceding Office action for a thorough discussion of the reasons.

Nevertheless, Applicants have reiterated the argument that Allan et al. teaches fine needle aspiration or a core biopsy were initially used to diagnose the study's subjects, who must have been diagnosed with breast cancer to participate in the study; although this is true, it is duly noted that the "take home" message is, radioimmunolocalization can be used as an alternative to fine needle aspiration and core biopsy. Contrary to Applicants' arguments, fine needle aspiration is not used to perform the radioimmunolocalization protocol described by Allan et al.

Applicants have continued to reiterate arguments that neither Hou et al. nor Allan et al. teach the claimed invention. Again, Applicants are reminded, one cannot show

nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicants have argued that there would have been no motivation to combine the teachings of Hou et al. and Allan et al. Again, the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, as discussed in previous Office actions, there is some teaching and suggestion found in the references themselves, which would have motivated the artisan of ordinary skill in the art at the time the invention was made to have practiced the claimed invention with a reasonable expectation of success.

Applicants have argued that the Examiner must have used hindsight to conclude the obviousness of the claimed invention. Again, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The Examiner did not rely upon knowledge gleaned from Applicants' disclosure to construct the rejection of the claims under 35 USC § 103(a); the Examiner only used knowledge that was within the level of ordinary skill at the time the claimed invention was made. Therefore, the rejection is proper.

12. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,168,779 A (Barsky et al.; '779) in view of Canto et al. (*Gastrointestinal Endoscopy* **44**: 1-7, 1996), Allan et al. *(British Journal of Cancer* **67**: 706-712, 1993), as evidenced by

Krag et al. (*New England Journal of Medicine* **339**: 941-946, 1998), and Lasfargues et al. (*Journal of the National Cancer Institute* **61**: 967-978, 1978).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Applicants are referred to the rejections above for an analysis of the claims.

Teachings and Suggestions of the Primary Reference

US 6,168,779 A ('779) teaches methods for accessing breast ducts by a procedure involving catheterization to facilitate the delivery of identifying agents that can be used to identify and thereby locate premalignant or malignant cancerous cells within or near a duct or orifice on a breast of a patient diagnosed with breast cancer. '779 specifically teaches that duct cannulation can be performed in which a catheter is inserted into the lumen of one or more pre-selected ducts on the breast of a patient (column 6, lines 37-42 and also claims 10, 18, and 27). Desired diagnostic material may then be instilled into the duct through the catheter inserted through the breast duct (column 6, lines 54-55). According to '779, a targeting molecule, such as an antibody capable of specifically targeting epithelial cells that display a particular marker on their surface and which is coupled to an identifying agent, such as a dye label, is an example of a diagnostic material that can be delivered to the patient through the breast duct (column 3, lines 4-17). A schematic of the method is provided in Figure 3, which illustrates that an orifice region of a ductal network can be identified and located "with a plurality of markers M lining the epithelium of the duct and extending to the perimeter of

the orifice" and "labeled antibodies A can be used to locate and label those markers M which are near the orifice O" (column 4, lines 63-67). '779 teaches "exemplary tissue markers include those present on the ductal epithelium" (abstract). '779 teaches, "an orifice to one or more ductal networks is labeled using a specific binding substance, typically an antibody, specific for a tissue marker present on the orifice" (abstract). Thus, '779 provides a genus of identifying agents that when coupled to a targeting agent that specifically recognizes and binds to a particular cellular marker can be delivered through one or more pre-selected breast ducts in an amount sufficient to identify and locate a species of epithelial cells that display that marker at the cell surface.

'779 does not expressly disclose that the diagnostic method can be used to identify the location of pre-malignant or malignant cancerous cells, *per se.* Nonetheless, '779 teaches that the diagnostic method can be used to identify a genus of epithelial cells, which includes pre-malignant and malignant ductal epithelial cells, that display a particular tissue marker or cellular antigen to which a targeting molecule coupled to an detectable, identifying agent, e.g., a radiolabeled antibody, will bind specifically to enable a clinician to identify the location of those cells. Therefore, it would have been understood by the artisan of ordinary skill in the art that the method could be used to identify the location of premalignant or malignant breast cancer cells in the breast ductal network, if the identifying agent is coupled to an antibody that binds specifically to an antigen displayed at the cell surface by the premalignant or malignant breast cancer cells.

'779 does not expressly disclose allowing any unbound identifying agent or coupled compound to be eliminated by natural absorption and clearance in the body so that its removal by the practitioner is not required. Although '779 does not explicitly teach allowing unbound portions of the delivered identifying agent to be eliminated from the breast duct, the elimination of the unbound portions of the identifying agent will occur naturally as a result of the process. The step of *allowing* the unbound portions of

the delivered identifying agent to be eliminated appears to be a passive step, i.e., allowing unbound portions to be eliminated appears to require no active step or participation by the practitioner. Practicing the method of '779 will inherently lead to allowing unbound identifying agent to be eliminated by natural processes.

Differences between the Teachings or Suggestions of the Primary Reference and the Claims at Issue

'779 does not expressly teach that the identifying agent, or the compound coupled to an identifying agent, which is bound to premalignant or malignant cells within the breast duct or breast ductal network can, or should be detected *after* the unbound portions of the identifying agent or compound are no longer present within the breast duct, as recited in claims 1 and 5. Similarly, '779 does not expressly teach that lymph node involvement should be determined *after* the unbound portions of the identifying agent or compound coupled to an identifying agent are no longer present within the breast duct, as recited in claims 9 and 13.

'779 does not expressly disclose that the identification of the cells can be for the purpose of excising tissue surrounding and including the cells. '779 does not disclose that the method can be used to determine whether there is lymph node involvement in patients diagnosed with pre-malignant or malignant cancer growths, wherein said method comprises a step of detecting the identifying agent in a sentinel lymph node.

Teachings and Suggestions of the Secondary Reference and the Level of Ordinary Skill in the Pertinent Art

Canto et al. teaches methylene blue is capable of binding selectively to pre-malignant, or dysplastic cells, and to malignant cells; Canto et al. demonstrates that methylene blue can be used to distinguish and localize premalignant or malignant epithelial cancer cells. Canto et al. teaches that after the step of delivering methylene blue and allowing methylene blue to bind premalignant or malignant cells, the tissue is washed to remove excess methylene blue. See entire document, but particularly the methods and materials section at page 2.

Therefore, although '779 does not expressly teach that the identifying agent, which is bound to premalignant or malignant cells within the breast duct or breast ductal network can, or should be detected after the unbound portions of the identifying agent or compound are no longer present within the breast duct, as recited in claim 5, the level of skill in the art at the time the invention was made was such that it would have been obvious to one of ordinary skill in the art to detect in a breast duct or breast ductal network, the presence of premalignant or malignant breast cancer cells, which are bound by an identifying agent, *after* washing the breast tissue to remove any unbound, or non-specifically bound identifying agent and/or *after* allowing any unbound bound identifying agent to passively diffuse out of the tissue. Canto et al., for example, teaches that *before* detecting premalignant or malignant cancer cells bound to the identifying agent, the excess, unbound identifying agent should be washed away from the anatomical site of the suspected lesion. Only after excess, unbound identifying agent is washed off, do Canto et al. disclose that the location of premalignant or malignant cancer cells bound by the identifying agent is determined. Therefore, it would have been understood by the artisan of ordinary skill at the time of invention that the presence of the unbound or non-specifically bound identifying agent in the tissue might produce undesirable levels of background, obscure detection of the premalignant or malignant cells within the tissue, and lead to false negative and/or false positive results.

Allan et al. teaches what was set forth in the 35 USC § 103(a) rejection above. As evidenced, by Krag et al., a sentinel lymph node is a regional lymph node; therefore, the method of Allan et al. can be used to determine lymph node involvement in a patient diagnosed with breast cancer, wherein an identifying agent is detectable in a sentinel lymph node. It is well known in the art that ductal breast cancer is of breast epithelial cell origin, as evidenced by the teachings of Lasfargues et al. Allen et al. teaches that the gene product of the proto-oncogene, *c-erbB-2* is over-expressed in breast cancer and is therefore an example of a breast epithelial tissue marker. Notably, the method of Allan et al. does not require the practitioner to remove the unbound coupled compound

comprising the radiolabeled antibody from the patient's body. Therefore, allowing the unbound coupled compound to be absorbed and cleared naturally by the body of the patient is implicit in the method of Allan et al.

Lasfargues et al. teaches ductal breast cancer is of breast epithelial cell origin.

The Obviousness of the Claimed Invention

Based on the teachings of Allen et al. and Lasfargues et al., it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made that an anti-ErbB2 antibody coupled to an identifying agent that specifically targets cancerous epithelial cells that over-express ErbB-2 within the breast duct can be used in the method of '779 to identify the location of malignant breast cancer within a breast duct or breast ductal network. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the identifying agent of Allan et al. in the method of '779, because the identifying agent of Allan et al. is coupled to a targeting molecule that enables the identifying agent to specifically target malignant breast cancer cells that over-express the marker to which the targeting molecule binds. One would have been motivated to use the identifying agent of Allan et al. in the method of '779 to identify of the location of malignant breast cancer cells expressing ErbB2 within the duct of a patient's breast and to determine whether or not there is lymph node involvement in the patient.

Response to Applicants' Remarks

Applicants have traversed the rejection of claims 1-16 under 35 USC § 103(a) for the reason set forth in section 18 of the previous Office action mailed May 7, 2003 (Paper No. 26), arguing, in particular, no motivation would have existed to combine the teachings of the cited references, impermissible hindsight had to have been used in determining the obviousness of the invention, and no reasonable expectation of successfully practicing the invention would have been had by one of ordinary skill in the art at the time the invention was made.

Applicants' remarks have been previously considered and were and still not found persuasive; therefore Applicants are referred to the preceding Office action for a discussion of the reasons. Additionally, Applicants are referred to the response to Applicants' remarks, which is set forth in the rejection above.

13. Claims 1-4 and 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hou et al. (*Radiology* **195**: 568-569, 1995) in view of Canto et al. (*Gastrointestinal Endoscopy* **44**: 1-7, 1996), McQuarrie et al. (*European Journal of Nuclear Medicine* **24**: 381-389, 1997), and Krag et al. (*New England Journal of Medicine* 339: 941-946, 1998).

look like further in view of Hou in view of canto as applied to claims 1-9

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Applicants are referred to the rejections above for an analysis of the claims.

Teachings and Suggestions of the Primary Reference

Hou et al. teaches that which was set forth in the rejection under 35 USC § 103(a) above. In addition, Hou et al. teaches that the contrast material is aspirated or expelled from the breast duct after mammography. See the entire document. See the previous Office actions.

Differences between the Teachings or Suggestions of the Primary Reference and the Claims at Issue

Hou et al. does not expressly disclose allowing any unbound identifying agent or coupled compound to be eliminated by natural absorption and clearance in the body so that its removal by the practitioner is not required, as recited in claims 1, 5, 9, and 13.

Although Hou et al. does not explicitly teach allowing unbound portions of the delivered identifying agent or compound comprising an identifying agent to be eliminated from the breast duct or lymph node, the elimination of the unbound portions of the agent or compound will occur naturally as a result of the process. The step of *allowing* the unbound portions of the delivered agent or compound to be eliminated appears to be a passive step, i.e., allowing unbound portions to be eliminated appears to require no active step or participation by the practitioner. Practicing the method of Allan et al. will intrinsically lead to allowing unbound identifying agent to be eliminated by natural processes, i.e., passive diffusion from the breast duct or breast ductal network into the lymphatic system and passive diffusion from the lymphatic system to the blood, which carries the unbound identifying agent to organs, e.g., liver and kidney, which act to "clear" the body of the unbound identifying agent.

Hou et al. does not expressly teach that the identifying agent, or the compound coupled to an identifying agent, which is bound to premalignant or malignant cells within the breast duct or breast ductal network can, or should be detected *after* the unbound portions of the identifying agent or compound are no longer present within the breast duct, as recited in claims 1 and 5.

In addition, Hou et al. does not expressly disclose that the method can be used to determine whether or not there is lymph node involvement in patients diagnosed with pre-malignant or malignant cancer growths, wherein said method comprises a step of detecting the identifying agent in a sentinel lymph node, as recited in claims 9 and 13. Hou et al. does not expressly teach that lymph node involvement should be determined *after* the unbound portions of the identifying agent or compound coupled to an

identifying agent are no longer present within the breast duct, as recited in claims 9 and 13. Hou et al. does not teach that an identifying agent that is coupled to a targeting molecule can be used in place of the identifying agent, not coupled to a targeting molecule, when practicing the diagnostic methods of claims 1 and 9.

Teachings and Suggestions of the Secondary Reference and the Level of Ordinary Skill in the Pertinent Art

Canto et al. teaches methylene blue is capable of binding selectively to pre-malignant, or dysplastic cells, and to malignant cells; Canto et al. demonstrates that methylene blue can be used to distinguish and localize premalignant or malignant epithelial cancer cells. Canto et al. teaches that after the step of delivering methylene blue and allowing methylene blue to bind premalignant or malignant cells, the tissue is washed to remove excess methylene blue. See entire document, but particularly the methods and materials section at page 2.

Therefore, although Hou et al. does not expressly teach that the identifying agent, which is bound to premalignant or malignant cells within the breast duct or breast ductal network can, or should be detected after the unbound portions of the identifying agent or compound are no longer present within the breast duct, as recited in claim 5, the level of skill in the art at the time the invention was made was such that it would have been obvious to one of ordinary skill in the art to detect in a breast duct or breast ductal network, the presence of premalignant or malignant breast cancer cells, which are bound by an identifying agent, *after* washing the breast tissue to remove any unbound, or non-specifically bound identifying agent and/or *after* allowing any unbound bound identifying agent to passively diffuse out of the tissue. Canto et al., for example, teaches that *before* detecting premalignant or malignant cancer cells bound to the identifying agent, the excess, unbound identifying agent should be washed away from the anatomical site of the suspected lesion. Only after excess, unbound identifying agent is washed off, do Canto et al. disclose that the location of premalignant or malignant cancer cells bound by the identifying agent is determined. Therefore, it would

have been understood by the artisan of ordinary skill at the time of invention that the presence of the unbound or non-specifically bound identifying agent in the tissue might produce undesirable levels of background, obscure detection of the premalignant or malignant cells within the tissue, and lead to false negative and/or false positive results.

McQuarrie et al. teaches a radioimmunoscintigraphic method for identifying the location of malignant breast cancer in patients comprising administering a radiolabeled antibody to the patient and acquiring images using a gamma camera. Specifically, McQuarrie et al. teaches that patients received 1, 2, or 4 mg of ^{99m}Tc-labeled monoclonal antibody that specifically binds a marker expressed by breast adenocarcinoma of epithelial origin (page 382, columns 1-2). Thus, patients were injected with a compound comprising a targeting molecule (i.e., an antibody) coupled to an identifying agent (i.e., a radioisotope). Serial blood samples were drawn before and after the injection of the antibody at successive intervals in order to determine serum clearance of the antibody in the body of the patient (page 382, column 2). Also, urine samples were collected at intervals following the injection in order to determine urinary clearance of the antibody in the body of the patient (page 382, column 2). McQuarrie et al. discloses that urinary excretion was predominant in patients (page 384, column 1). McQuarrie et al. also teaches, "on a per patient basis radioimmunoscintigraphy (RIS) showed both a sensitivity and a positive predictive value of 96%" and that "eighty-six lesions were scored as true-positive in the total patient population" (page 385, column 2). McQuarrie et al. conclude, "the ability of this monoclonal antibody to detect tumour both in the primary site and in regional lymph nodes is a significant clinical advantage" (page 387, column 1). The method of McQuarrie et al. does not require the practitioner to remove the unbound radiolabeled antibody from the patient because the antibody is absorbed or naturally clears in the body. See the entire document.

Although McQuarrie et al. does not explicity teach that the regional nodes in which the cancer cells can be detected are the sentinel nodes, Krag et al. teaches the first stop along the route of lymphatic drainage from a primary tumor is a limited set of

regional lymph nodes and that the lymph nodes that first receive drainage from a tumor are termed sentinel nodes.

The Obviousness of the Claimed Invention

Given the teachings of the prior art, as a whole, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the radiolabeled antibody of McQuarrie et al. for the contrast agent of Hou et al. in the method of Hou et al. in order to identify the location of malignant breast cancer in the body of a patient, because Hou et al. teaches a method of delivering the antibody directly to the anatomical site where the clinician expects to find cancerous cells and thus, requires less antibody be administered to the patient since not as much of the antibody will be absorbed by non-targeted tissues (e.g., the kidneys) and because McQuarrie et al. teaches that the antibody can be used successfully to localize malignant breast cancer in a patient and furthermore, does not require the practitioner to remove unbound antibody from the patient since the unbound antibody is absorbed and cleared in the body of the patient. One would have been motivated to substitute the radiolabeled antibody of McQuarrie et al. for the contrast agent of Hou et al. in the method of Hou et al. because the specificity of the antibody will enable superior accuracy in localizing the malignancy for the purpose of excising the diseased tissue and because the antibody does not have to be removed by the practitioner from the body of the patient, thus simplifying the procedure.

Response to Applicants' Remarks

Applicants have traversed the rejection of claims 1-16 under 35 USC § 103(a) for the reason set forth in section 19 of the previous Office action mailed May 7, 2003 (Paper No. 26), arguing, in particular, no motivation would have existed to combine the teachings of the cited references, impermissible hindsight had to have been used in determining the obviousness of the invention, and no reasonable expectation of successfully practicing the invention would have been had by one of ordinary skill in the art at the time the invention was made.

Applicants' remarks have been previously considered and were and still not found persuasive; therefore Applicants are referred to the preceding Office action for a discussion of the reasons.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1-16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 31, and 32 of co-pending Application No. 09/565,642 in view of Slavin-Chiorini et al. (*Cancer Biotherapy & Radiopharmaceuticals* **12**: 305-316, 1997), Allan et al. *(British Journal of Cancer* **67**: 706-712, 1993), and Krag et al. (*New England Journal of Medicine* 339: 941-946, 1998) for the reason set forth in section 21 of the previous Office action mailed May 7, 2003.

Applicants have remarked that a terminal disclaimer may be filed at the time the claims in either or both applications are indicated to be allowable. Accordingly, this issue is to be held in abeyance until such a time that there is allowable subject matter in this application.

Conclusions

16. No claims are allowed.

17. The prior art made of record and not relied upon is considered pertinent to Applicants' disclosure. Dietler et al. teaches localization of nonpalpable breast lesions. Gill et al. teaches selective staining of bladder tumors. Love et al. teaches intraductal cannulation and breast duct endoscopy. Saarela et al. teaches methylene blue staining of breast lesions.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
December 4, 2003

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600